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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data was collected using commercially available programs such as Flow-Jo, Bio-rad Image Lab, Image J, Applied Biosystems Real time Applications, etc.
Data analysis	Data analysis was done using Graphpad Prism (Version 5) and Microsoft Excel.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Sample sizes were determined using the minimum number of animals necessary to observe statistically significant changes in a certain animal model given the observed within group variability.
Data exclusions	In most cases no data was excluded. In some instances however, outliers based on pre-established criteria (three standard deviations from the mean) were excluded and likely due to measurement of procedural errors.
Replication	Replicates were included in every study; in vitro assays were replicated to ensure reproducibility and animal studies included used sufficient animals numbers. Furthermore, several CDC-donors were used in this study to ensure generalizability of the findings.
Randomization	Animals were assigned to different groups randomly.
Blinding	Animal procedures, echo acquisition and analyses, and histological analyses were done in a blinded manner. Exceptions include echo data in Figures 2k and 5f-h which the were analyzed in a non-blinded setting.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Antibody Names Primary/Secondary Company Catalog Numbers.
Pan-Actin (D18C11) Rabbit mAb-HRP Conjugated Primary Cell Signaling Technology 12748
GAPDH Rabbit mAb-HRP Conjugated Primary Cell Signaling Technology 14C10
Anti-Mest Rabbit Polyclonal Antibody Primary Abcam ab230114
EXTL1 Polyclonal Antibody Primary Thermo Fisher Scientific PA5-72069
Anti-Rabbit IgG, HRP-Linked Antibody Secondary Cell Signaling Technology 7074
Anti-Rabbit IgG, HRP-Linked Antibody Secondary Cell Signaling Technology 7074
FITC Mouse Anti-Human CD90 Primary BD Pharmingen 555595
Human Endoglin/CD105 Fluorescein-conjugated Antibody Primary R&D Systems FAB10971F
LRP5/6 Polyclonal Antibody, FITC Conjugated Primary Bioss Bs-2905R-FITC
Human DDR2 Antibody Primary R&D Systems MAB25381
FITC Mouse Anti-Human CD45 Primary BD Pharmingen 555482
PE Mouse Anti-Human CD44 Primary BD Pharmingen 555479
PE Mouse Anti-Human CD29 Primary BD Pharmingen 555443
FITC Mouse IgG1, κ Isotype Control Primary BD Pharmingen 555748
PE Rat IgG2b, κ Isotype Control Primary BD Pharmingen 553989

Validation

Links to validation information for antibodies are available below. These include sample blots for the protein indicated.
https://www.cellsignal.com/products/antibody-conjugates/pan-actin-d18c11-rabbit-mab-hrp-conjugate/12748

https://www.cellsignal.com/products/antibody-conjugates/gapdh-14c10-rabbit-mab-hrp-conjugate/3683
https://www.abcam.com/mest-antibody-ab230114.html
https://www.thermofisher.com/antibody/product/EXTL1-Antibody-Polyclonal/PA5-72069
https://media.cellsignal.com/coa/7074/28/7074-lot-28-coa.pdf
http://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/fitc-mouse-anti-human-cd90-5e10/p/555595
https://www.rndsystems.com/products/human-endoglin-cd105-fluorescein-conjugated-antibody-166707_fab10971f
https://www.biossusa.com/products/bs-2905r-fitc
https://www.rndsystems.com/products/human-ddr2-antibody-290804_mab25381
https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/fitc-mouse-anti-human-cd45-hi30/p/555482
https://www.bdbiosciences.com/us/applications/research/t-cell-immunology/t-follicular-helper-tfh-cells/surface-markers/human/pe-mouse-anti-human-cd44-g44-26-also-known-as-c26/p/555479
https://www.bdbiosciences.com/us/applications/research/stem-cell-research/cancer-research/human/pe-mouse-anti-human-cd29-mar4/p/555443
https://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-human-antibodies/cell-surface-antigens/fitc-mouse-igg1-isotype-control-mopc-21/p/555748
http://www.bdbiosciences.com/us/reagents/research/antibodies-buffers/immunology-reagents/anti-mouse-antibodies/cell-surface-antigens/pe-rat-igg2b-isotype-control-a95-1/p/553989

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Cardiosphere-derived Cells (CDCs) and normal human dermal fibroblasts (NHDFs)
Authentication	For NHDFs, cell line authentication was done by the commercial supplier (ATCC). CDCs were collected from primary human tissue (deceased organ donors supplied by the National Development & Research Institutes, Inc) and processed by Capricor Therapeutics.
Mycoplasma contamination	Cells used in this study were negative for myocoplasma contamination as shown in the certificate of analysis. Some CDC donors in this study had not been tested.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified lines were used in this study.

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Cells were harvested and counted (2x10^5 cells per condition). Cells were washed with 1% bovine serum albumin (BSA) in 1x phosphate-buffered saline (PBS) and stained with the appropriate antibody (BD Pharmingen) for 1 hr at 4˚C. Cells were then washed again and resuspended in 1% BSA in 1x PBS. BD Cytofix/CytopermTM kit was used for cell permeabilization before staining.
Instrument	Data collection was done using a BD FACS Canto™ II instrument and Sony SA3800 Spectral Analyzer
Software	Data analysis was done using FlowJo v10 Workspace and Sony SA3800 Analyzer Software
Cell population abundance	Cell viability was between 80-95% in post-sort fractions. Non-viable cells were excluded from analysis based on FSC/SSC gating strategy.
Gating strategy	Positive and negative gates were determined based on the isotype antibody sample.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.